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Peer Review

Review of: "Role of Inflammation in the Pathogenesis of Anemia in Chronic Kidney Disease: Exploring the Impact of Inflammatory Biomarkers on Erythropoiesis and Erythropoietin Response"

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This clinical study aimed to investigate the effect of inflammation on patients with chronic kidney disease undergoing hemodialysis, particularly concerning the current understanding of anemia. The study highlighted that inflammatory biomarkers might interfere with erythropoiesis and the response to erythropoietin (EPO), potentially serving as predictors of EPO resistance or anemia staging. The manuscript is well-written and clinically relevant; however, certain critical aspects were not adequately addressed. Notably, exclusion criteria were not comprehensively considered, and the weak correlation, the absence of other co-associated inflammatory markers, and the lack of robust statistical analyses weaken the clarity and fundamental evidential strength of the conclusions drawn. Therefore, I recommend this study for a **major review**.

CRP Half-Life and Potential Confounders

- C-reactive protein (CRP) has an approximate half-life of **18–20 hours**, being degraded and cleared by the liver as inflammation subsides. Do the authors provide details on how CRP was measured? Were its degradation rate and half-life considered in the analysis? Additionally, CRP levels are influenced by comorbidities such as **obesity**, which can significantly alter baseline CRP levels among patients. Given this, was obesity considered as an exclusion factor in the analysis?

IL-6, JAK/STAT3 Pathway, and EPO Resistance

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- It is well established that **IL-6 activates the JAK/STAT3 pathway in hepatocytes**, promoting CRP synthesis, which in turn has been associated with **EPO resistance**. Furthermore, the activation of the **JAK/STAT3 pathway in erythroid precursors within the bone marrow** contributes to EPO resistance by:

  i) Increasing **hepcidin** expression, thereby reducing iron bioavailability.

  ii) Directly inhibiting erythropoiesis by impairing erythroblast proliferation and differentiation.
- Given these mechanistic insights, **IL-6 quantification is crucial** for correlating inflammation with anemia or EPO resistance. Do the authors provide data on IL-6 levels in the studied cohort?

Multivariate Logistic Regression Analysis

- Methodologically, a **multivariate logistic regression analysis** should have been performed with **EPO resistance as the dependent variable** in both groups, calculating **odds ratios (ORs) for all potentially associated variables** to assess their role as independent predictors. Do the authors report the OR values for these associations?

Strength of Correlations and Statistical Rigor

- The reported **positive and negative correlations between CRP and hematologic/erythrocytic parameters** appear to be weak-to-moderate, raising concerns regarding its robustness as a predictor of **EPO resistance or anemia severity**. I strongly recommend a **reassessment of statistical analyses and group stratification** to refine the associations between inflammation-related variables and anemia outcomes.

Declarations

Potential competing interests: No potential competing interests to declare.